METHODS OF UPREGULATING TIPARP AS ANTICANCER STRATEGIES

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of priority from U.S. Provisional Application No. 62/702,634, filed Jul. 24, 2018, the entire contents of which are incorporated herein by reference.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] This invention was made with government support under Grant Nos. GM086703 and OD018516, awarded by the National Institutes of Health. The government has certain rights in the invention.

INCORPORATION BY REFERENCE OF SEQUENCE LISTING

[0003] The Sequence Listing in an ASCII text file, named as 36450PCT_8342_02_PC_SequenceListing.txt of 8 KB, created on Jul. 24, 2019, and submitted to the United States Patent and Trademark Office via EFS-Web, is incorporated herein by reference.

BACKGROUND

[0004] ADP-ribosylation is a reversible protein post-translational modification (PTM) that transfers a single, or multiple ADP-ribosyl groups to substrate proteins (Gibson, B. A. & Kraus, W. L., *Nat Rev Mol Cell Biol* 13, 411-424, (2012)). Intracellular ADP-ribosylation is catalyzed by the ADP-ribosyltransferase diphtheria toxin-like (ARTDs), commonly known as poly-ADP-ribose polymerases (PARPs) (Hottiger, M. O., et al. *Trends Biochem Sci* 35, 208-219, (2010)). Compared to poly-ADP-ribosylation, the function of intracellular mono-ADP-ribosylation is less understood. Nevertheless, it is becoming evident that mono-ADP-ribosylation modulates important signaling pathways and it has been linked to numerous diseases, including inflammation, diabetes, neurodegeneration, and cancer (Corda, D. & Di Girolamo, M. *EMBO J* 22, 1953-1958, (2003); Butepage, M., et al., *Cells* 4, 569-595, (2015); Corda, D. & Di Girolamo, M., *Sci STKE* 2002, pe53, (2002); Del Vecchio, M. & Balducci, E. *Mol Cell Biochem* 310, 77-83, (2008); Scarpa, E. S., Fabrizio, G. & Di Girolamo, M. *FEBS J* 280, 3551-3562, (2013).). Tetrachlorodibenzo-p-dioxin (TCDD)-inducible poly (ADP-ribose) polymerase (TiPARP, also known as PARP7 or ARTD14) is a mono-ADP-ribosyltransferase (MacPherson, L. et al. *Nucleic Acids lies* 41, 1604-1621, (2013)) and TiPARP was first identified as a target gene of and hydrocarbon receptor (AHR) in response to the dioxin TCDD (Ma, Q. *Arch Biochem Biophys* 404, 309-316 (2002); Ma, Q. et al, *Biochem Biophys Res Commun* 289, 499-506, (2001)). Once expressed, TiPARP regulates transcriptional activity of AHR and liver X receptor via ADP-ribosylation (MacPherson, L. et al. *Nucleic Acids Res* 41, 1604-1621, (2013); Bindesboll, C. et al. *Biochem J* 413, 899-910, (2016)). However, the detailed function of TiPARP and its role in modulating transcription was not well understood. The transcriptional activity of both AHR and HIF-1α require their bindings with the co-activator HIF-1β (also known as and hydrocarbon receptor nuclear translocator, ARNT), as well as the recognition of GCGTG core sequence on target genes (Semenza, G. L. & Wang, G. L. *Mol Cell Biol* 12, 5447-5454 (1992); Jiang, B. H. et al., *J Biol Chem* 271, 17771-17778 (1996); Wang, G. L. et al., *Proc Natl Acad Sci USA* 92, 5510-5514 (1995)). Structurally, they both contain the basic-helix-loop-helix (bHLH)-PAS motif that is essential for their heterodimerization with HIF-1β (Jiang, B. H. et al., *J Biol Chem* 271, 17771-17778 (1996); Wang, G. L. et al., *Proc Natl Acad Sci USA* 92, 5510-5514 (1995)). The similarity between AHR and HIF-1α prompted us to investigate the connection between HIF-1 and TiPARP. Activated HIF-1 is a key regulator of oxygen homeostasis that mediates adaptive responses to changes in oxygenation through transcriptional activation of genes involved in glucose metabolism and cell survival (Gordan, J. D. & Simon, M. C. *Curr Op in Genet Dev* 17, 71-77, (2007); Semenza, G. L. *Nat Rev Cancer* 3, 721-732, (2003)). Due to intratumoral hypoxia and genetic mutations, HIF-1α is stabilized or overexpressed in human cancers and is often associated with increased mortality in cancer patients (Semenza, G. L. *Nat Rev Cancer* 3, 721-732, (2003); Semenza, G. L. *Genes Dev* 14, 1983-1991 (2000); Masoud, G. N. & Li, W. *Acta Pharm Sin B* 5, 378-389, (2015)).

SUMMARY OF THE DISCLOSURE

[0005] The present disclosure is directed to methods for treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a TiPARP agonist. In particular embodiments, the TiPARP agonist interacts with TiPARP directly. In some embodiments, the TIPARP agonist may be an agent that leads to elevated expression of the TiPARP protein. In other embodiments, the TIPARP agonist is an expression vector encoding an exogenous TiPARP protein, or more particularly, wherein the expression of the exogenous TiPARP is inducible. The TiPARP agonist may be, for example, a tamoxifen compound (e.g., tamoxifen or derivative thereof), flavone or derivative thereof, isoflavone or derivative thereof, diindolylmethane compound, or chlorinated dibenzo-p-dioxin (CDBD) compound or derivative thereof. The cancer being treated may be associated with an elevated expression of HIF-1a. The cancer may be selected from, for example, breast cancer, colon cancer, lung cancer, skin cancer, brain cancer, blood cancer, cervical cancer, liver cancer, prostate carcinoma, pancreas carcinoma, gastric carcinoma, ovarian carcinoma, renal cell carcinoma, mesothelioma, and melanoma. The cancer may, in some embodiments, be other than breast cancer, such as lung or colon cancer.

[0006] In some embodiments, the disclosure is directed to a method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a TiPARP agonist.

[0007] In some embodiments, the TiPARP agonist is an aryl hydrocarbon receptor (AHR) agonist. In some embodiments, the TiPARP agonist is an estrogen receptor (ER) agonist.

[0008] In some embodiments, the TiPARP agonist interacts with TiPARP directly.